

Exhibit 35

**EXPERT REPORT OF R. COREY WALLER,
M.D., M.S.**

Dated: August 3, 2020

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II. Background and Credentials

I, R. Corey Waller MD, MS, FACEP, am an addiction, pain, and emergency medicine specialist and hold a Master of Science in Biology with a neuro-molecular focus. I am the Editor in Chief for the American Society of Addiction Medicine (ASAM) criteria, the most widely used and comprehensive set of guidelines for patient placement, continued to stay, transfer, or discharge of patients with addiction and co-occurring conditions. I am currently board certified in emergency medicine and addiction medicine and a coauthor of the American Society of Addiction Medicine's *Handbook on Pain and Addiction*, Oxford Press 2018, including the author of its chapter "The Neuroscience of Pain and Addiction." I have also served in various other roles within the American Society of Addiction Medicine, including the chair of the Legislative Advocacy Committee. In that role, I was called upon to testify before the United States Congress regarding opioid addiction and its treatment. In addition to my work on the national level, I formerly served as the President of the Michigan Society for Addiction Medicine, was appointed to the State of Michigan Opioid Task Force, and authored and implemented the State of Michigan's Medication Assisted Treatment Guidelines for Opioid Use Disorder in 2014. I am currently a principal at the Health Management Associates Institute on Addiction, an independent, national research and consulting firm specializing in publicly funded healthcare reform, policy, programs, and financing. Over the last two years, I have worked with over 30 health systems around the United States to address the opioid epidemic in numerous communities, with a focus on determining the root causes of the impact of opioids on public health and safety, addressing the severe impact on public health and safety of the opioid epidemic and developing treatment ecosystems for addiction (primarily to opioids), addressing

issues related to pain and behavioral health, as well as addressing various components of public health and safety, including the implementation and expansion of addiction treatment in the California prison system, developing addiction evaluation and treatment in multiple emergency departments in conjunction with the California bridge program, development of a board certification training pathway for physicians working in the California Department of Corrections and Rehabilitation, co-editing a perinatal best practices website with Stanford University, and expansion of ecosystems of treatment in multiple counties in California, Michigan, Pennsylvania and Ohio. In January of 2020, I became the Editor and Chief of the ASAM Criteria, which is the national guide to treatment planning and level of care determination for the field of addiction. In this role, I have worked with most state licensing departments and national payors to develop a cohesive approach to addiction treatment.

Prior to joining HMA, I served as the senior medical director for education and policy at the National Center for Complex Health and Social Needs in Camden, New Jersey, where I was responsible for developing and maintaining all training and in-person technical assistance delivered by the National Center in the areas of addiction, pain, and behavioral health treatment system development, payment model implementation, and healthcare policy. Before joining the National Center, I worked for the Spectrum Health System in Grand Rapids, Michigan, which is a fully integrated health system with 12 hospitals and over 1,000 employed physicians. I was the medical director of the Spectrum Health Medical Group Center for Integrative Medicine, the medical staff chief of pain medicine to the Spectrum Health Hospital System, as well as substance use disorder medical director at Lakeshore Regional Partners (Community Mental Health-Region 3). I have also worked extensively with local, state, and federal law enforcement

on the issues of controlled substance diversion and interdiction. In this role, I worked with the Federal Protective Service as a tactical physician, supporting force protection duties and servicing warrants in the Washington, D.C. area. I also served as the medical director for the Grand Rapids Police Department's Special Response Team (SRT). In this role, I participated in direct action against drug trafficking operations in Western Michigan, delivered support and strategic guidance for cooperative interdiction, and delivered direct medical care when needed to involved law enforcement personnel.

In addition, I have been involved in professional education regarding opioid addiction in a variety of settings and in many instances, that role has involved developing and delivering educational programs that help reverse misconceptions about opioid use and opioid use disorder (OUD). This has included testifying to the United States Congress and the Michigan State legislature, delivering keynote addresses at multiple national meetings, designing and writing the pain and addiction curriculum for the American Society of Addiction Medicine and building a Robert Wood Johnson Foundation-funded learning management system focused on interdisciplinary education for pain, addiction, and behavioral health. This work has required me to examine carefully how current misconceptions arose to develop effective counter-messages.

My curriculum vitae, a copy of which is **Schedule 3** to this report, describes my education, background, and qualifications more fully. I have authored or coauthored numerous publications, the title and citations of which are listed on my curriculum vitae (**Schedule 3**).

III. Topics for Opinions

I have been retained by the Plaintiffs, the Cabell County Commission and City of Huntingtonⁱ, to offer expert testimony in the matter titled *Cabell County Commission and City of Huntington, West Virginia v. AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation*,ⁱⁱ Case Nos. 1:17-op-45053-DAP and No. 1:17-op-45054. I was asked by the Plaintiffs to offer my professional opinions on a series of questions including:

- A. What are opioids?
- B. How do they work?
- C. Describe opioids' interaction with the body's natural pain system.
- D. What are the risks, if any, associated with opioids?
- E. Did the use and availability of opioids in the United States change over time? If yes, in what way?
- F. What were the consequences, if any, of any change in use and availability of opioids?
- G. What is the main cause of those consequences?
- H. Do we see those consequences prevalent in the Cabell-Huntington Community?
- I. Have opioids had a significant impact on public health in the Cabell-Huntington Community?
- J. Have opioids had a significant impact on public safety in the Cabell-Huntington Community?

ⁱ Throughout this Report, I will refer collectively as "the Cabell-Huntington Community" or "Plaintiffs.

ⁱⁱ AmerisourceBergen Drug Corporation, Cardinal Health, Inc., and McKesson Corporation will be collectively referred to as "Defendants" throughout this Report.

K. What are the standards for treating opioid addiction?

The next section will address these questions and offer my professional opinions related to these questions. My opinions are set forth below and are based on my knowledge, training and experience, as well as any of the literature, publications and data cited in this Report and the Schedules thereto. My opinions are stated to a reasonable degree of medical certainty.

In addition to my skill, knowledge, education, experience, and training, the basis for the facts and opinions upon which I will testify is my review of the relevant medical literature, public documents, and the deposition testimony provided in this case. Attached as **Schedule 4**, and cited throughout the Report and in the Endnotes thereto, is a list of the materials I considered in forming my opinions in this Report. I also received and reviewed the Expert Report of Craig McCann, PhD, CFA, the Expert Report of Katherine Keyes, PhD, the Expert Report of Lacy R. Keller, the Expert Report of James E. Rafalski and the Expert Report of Professor Thomas McGuire, all which inform and support my opinions as noted throughout this Report.

I reserve the right to amend or supplement the facts and opinions upon which I am expected to testify as additional information is made available.

IV. Compensation

My employer, Health Management Associates, is being compensated for my work in this case at the following rate: \$750 per hour.

V. Prior Testimony and Publications

I have not testified in any litigation matters during the last 4 years as an expert at trial or by deposition. A list of publications I authored within the last ten years is included as part of Schedule 3.

VI. Opinions

A. What are opioids?

The term “opioid” refers to naturally produced substances in the body (such as endorphins, enkephalins, dynorphins, and endomorphins) that bind, through molecular interaction, to opioid receptors. One of the primary effects of opioid activity in the body is to achieve analgesia when the body experiences pain.¹ The term “opioids” also refers to a class of exogenous chemicals that attempt to mimic the body’s natural substances to produce analgesia. Throughout my report, I will refer to “opioids” as exogenous opioids unless otherwise specified.

There are four separate subclasses of opioids:

1. **Endogenous opioid peptides:** These are the body’s naturally produced opioids and include molecules such as endorphins, enkephalins, dynorphins, and endomorphins.²
2. **Naturally occurring opiates and their esters:** These are the compounds that are directly linked to the opium poppy and include molecules such as morphine, codeine and thebaine.²
3. **Semisynthetic opioids:** These are created from the naturally occurring opiates and their esters and include diacetylmorphine (heroin), oxycodone, hydromorphone, and

hydrocodone. These opioids have the same basic chemical structure and contain the same basic chemical architecture as morphine and heroin.^{3,4}

4. **Synthetic opioids:** These are opioids that are fully laboratory-derived. While able to actively bind the opioid receptors, they have a different core chemical structure than both naturally occurring and semisynthetic opioids and include substances such as fentanyl, methadone, and tramadol.³⁻⁶

I have reviewed the Expert Report of Craig J. McCann, Ph.D., CFA, I understand that from 2006 to 2014 the three Defendants in this case were primarily engaged in the sale and shipment of semisynthetic opioids, including oxycodone and hydrocodone (herein I will refer to the drugs Defendants' sold and shipped listed in Dr. McCann's report generally as "Defendants' Drugs"). According to Dr. McCann's report, oxycodone and hydrocodone accounted for 85.9% of all dosage units in the transactions in Cabell County and Huntington City, West Virginia from 2006 to 2014 (McCann Report at Appendix 6a).⁷

1. The Body's Natural Opioids

The body's production and homeostasis of endogenous opioid peptides is complex and multifaceted, involving complex molecular structures and numerous systems throughout the body. It is important to understand the complexity of how the body uses its endogenous opioids in order to understand how attempts to replicate the body's natural system within man-made opioid drugs have fallen so disastrously short. Importantly, the body releases its natural opioid peptides to address the particular stress or physical or emotional challenge in a balanced and proportional fashion, without causing negative consequences such as respiratory suppression,

dysphoria or the disproportionate euphoria that have been all too commonplace with exogenous opioids, including Defendants' Drugs⁸⁻¹⁰ (*see Sections C&D, below*).

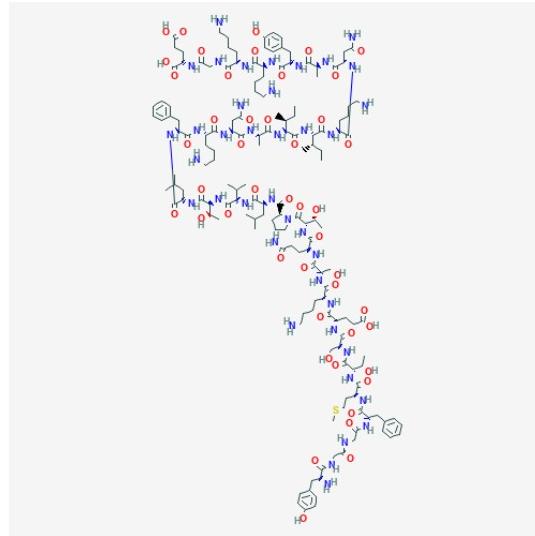
There are three main naturally occurring opioid peptides that are produced in the body:

Endorphin:

Derived from the hormone prepro-opiomelanocortin, endorphin was identified in the 1970s and is "the body's morphine." This molecule is released when the body is presented with a physical or emotional challenge. This can be due to physical exertion (the fabled "runner's high"), but the molecule also acts during the experience of pain to produce analgesia.^{2,11}

The primary receptor for endorphins is the mu-opioid receptor. This receptor functions in both the central and peripheral nervous system and is responsible for analgesia, respiratory depression, QT prolongation, sedation, slowed gastrointestinal transit in the modulation of hormones, and neurotransmitter release. This receptor is also the primary opioid receptor responsible for the processing of reward and producing euphoria.¹²⁻¹⁵

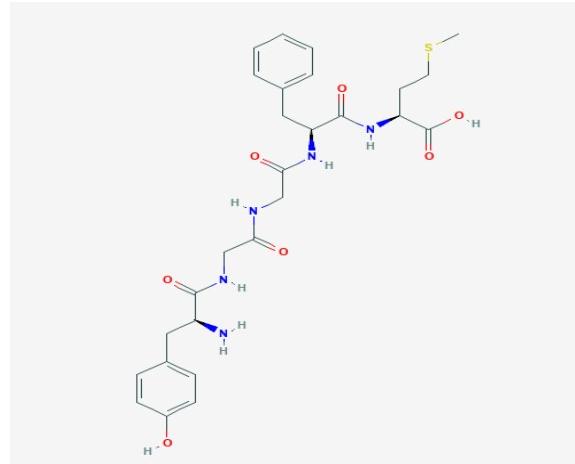
Because the structure of endorphins is so sophisticated, they can bind to the mu-opioid receptors in the body and allow for a predictable decrease in pain, mild euphoria, and stress relief without the negative side effects such as respiratory suppression, dysphoria or disproportionate sense of reward present with exogenous opioids, including Defendants' Drugs (*see Sections 4-5, below*). Indeed, the endorphin molecule is so complex that it can morph or fold into slightly different configurations allowing it to impact its affinity and potency for a given situation.¹⁶



This innate ability, when coupled with a G-protein type receptor like the mu-opioid receptors to which they bind, provides for almost infinite adaptability and adjustment to a given situation, and avoids the negative consequences seen with exogenous opioids such as oxycodone, hydromorphone and morphine.

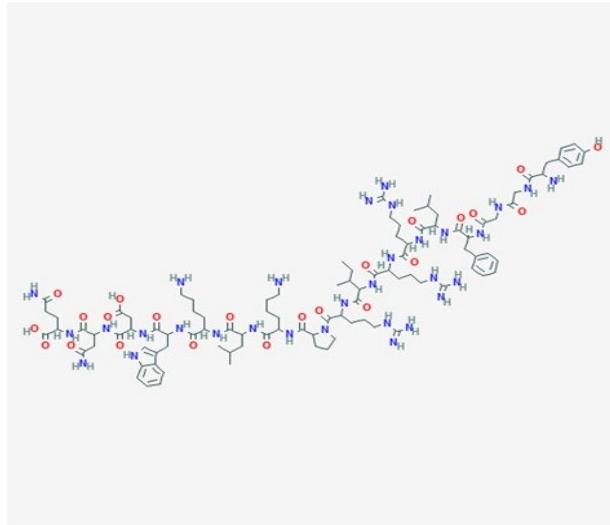
Enkephalin:

Enkephalin is derived from prepro-enkephalin, with a distribution of enkephalin into the brainstem and the spinal cord. It binds preferentially to the Delta opioid receptor but also to the mu-opioid receptor.^{2,11} Like endorphin, enkephalin can produce analgesia. It also likely plays a significant role in mood stabilization and an individuals' response to pain. Its structure is less complicated than endorphin; however, like endorphins, enkephalins importantly possess the capability to modify how they bind to the Delta and mu-opioid receptors given different physiologic stressors and, thus, adapt to a painful situation without creating tolerance, dysphoria or risk of addiction.¹⁴



Dynorphin:

Dynorphins are derivatives of the hormone prepro-dynorphin, and preferentially bind primarily to the Kappa-opioid receptor. Dynorphins play less of a role in the modulation of pain and instead focus on emotional control and the stress response to pain.^{17,18} Like the other endogenous opioid peptides, their complexity allows for them to meet a given situation physiologically. This property allows them to have a modified impact when binding to Opioid receptors and avoids long-term tolerance and hyperalgesia.



When the body experiences a painful stimulus, its natural systems for moderating pain bring to bear a multidimensional approach to pain that includes complex endogenous opioid peptides, a multitude of opioid receptor subtypes, and a number of structures of the brain and central nervous system. The body's natural response to pain includes sending signals along basic tracts (ascending and descending tracts) from the body to the brain and back down (*see Schedule 2*). Once the body has naturally processed a pain signal, it can make an almost infinite number of modifications to a given pain stimulus to ensure that the pain response is appropriate for the situation. This process occurs by an initial signal sent from the point of injury through nerve endings to the dorsal horn of the spinal cord. There the pain is modulated, based on a number of factors, and a signal is sent to the brain through ascending tracts that communicate pain signals to the brain (*see Schedule 2*).¹⁹⁻²⁴

Once a pain signal reaches the brain, the body's natural response, including endorphins, enkephalins and dynorphins, are released in the proper amounts to create the most advantageous response to the pain. (*See Schedule 1* for the basic brain structures involved with pain and addiction). All of the combined information created by differential binding of the mu,

kappa and delta receptors; the release of serotonin and norepinephrine from the amygdala; the thalamic modulation; and a multitude of other interactions, create a response that is then sent back from the brain down descending tracts – one set that inhibits the pain signal (the Descending Inhibitory Tracts) and one that excites the pain signal (the Descending Excitatory Signal).¹ The first serves as the brake pedal, helping to modulate the intensity of the pain signal coming from the brain, and the other serves as a gas pedal, helping to amplify the pain signal coming from the brain. Together, the balance of the gas and the brakes determines the intensity of the pain. In a normal pain situation, without opioids, these signals allow a person to assess, process, and cope with the pain appropriately. Over time, the natural system provides for adaptation of mood, physical activity, and ongoing tolerance of pain so that the body's physical and mental function is optimized.^{10,25}

One of the main reasons that external opioids, such as Defendants' Drugs, have caused such disastrous consequences is that they cannot mimic this complex and incredibly nuanced system for responding to pain, nor can these drugs do so without generating a host of extremely negative consequences.²⁶⁻³⁰ For example, the body's response to each pain situation is so nuanced that it can allow for wide ranging responses to pain, such as suppressing the pain of a gunshot wound so that a soldier can finish the fight, allow for a mother to deliver a child without pain control, and even making a person lose consciousness so that they do not have to experience the overwhelming severity of life-ending pain.

External opioids, by contrast, do not address individual pain situation nuances. In fact, they are so narrowly designed that the system cannot properly adapt to the painful stimuli. The

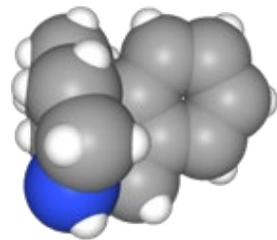
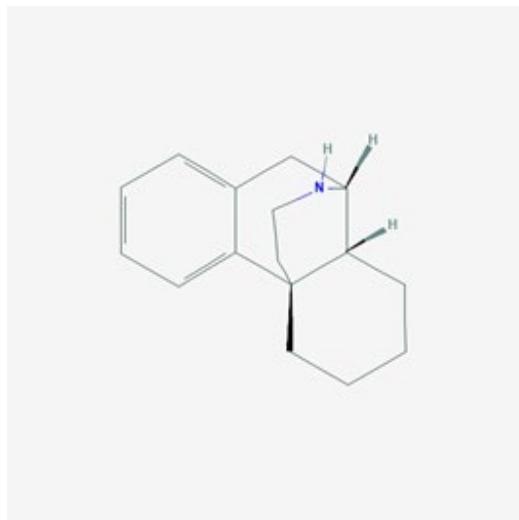
Defendants' Drugs only target a small binding area on the mu receptor and do not modulate all of the other systems.

Additionally, as explained in greater detail in Sections B-K below, external opioids trigger inappropriate and dangerous responses that are not triggered by the body's own endogenous opioid system. These responses cause real and serious consequences, such as addiction, tolerance, overdose, and death that are not outweighed by the benefits of Defendants' Drugs for long-term pain or outside of palliative care. (See Section E, below)

2. Opioid Drugs- The Molecule

The primary man-made attempts to create an opioid analgesic to treat pain, from morphine, to heroin, to Defendants' Drugs, are derived from a common core molecule, the four ring T-shaped molecule (morphinan or "the Molecule") depicted here:

Morphinan:



While drugs like morphine can be extracted from the Opium poppy (*Papaver somniferum* L.) and are physiologically active, semisynthetic opioids are merely derivatives of these molecules. The "core" of all opium-derived drugs is the morphinan ring structure.^{31,32} The

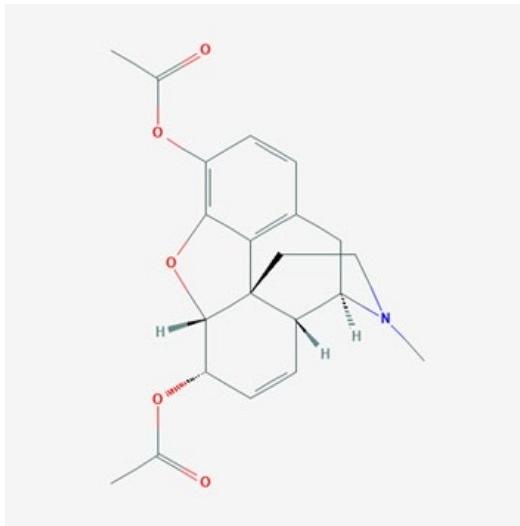
morphinan molecule is the synthetically derived core structure for the most commonly used modern semisynthetic opioids (including Defendants' Drugs). Morphinan, by itself, is not physiologically active but is the substrate by which other semisynthetic opioids are produced. All of these derivatives have had repeated, devastating and predictable consequences. That is because each of these drugs, including Defendants' Drugs, have this molecule as their base chemical structure. Due to the simplistic approach that this Molecule takes to the treatment of pain, and the ease with which it stimulates the reward system, it has been predictably risky. With the addiction crises associated with morphine and heroin in the late 1800s and early 1900s (both derivatives of morphinan), the pharmaceutical industry should have learned their lesson.³³ Indeed, by at least the 1980s, it was utterly predictable that Defendants' Drugs, derived from the same molecule, would wreak havoc in the same way that the Molecule has throughout history.

One of the earliest opiates that caused large scale problems with addiction, abuse, respiratory depression, and death was opium. Indeed, throughout history, there were intense periods of abuse and addiction to opium.

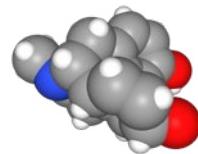
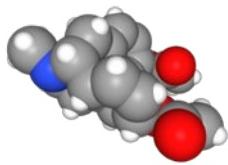
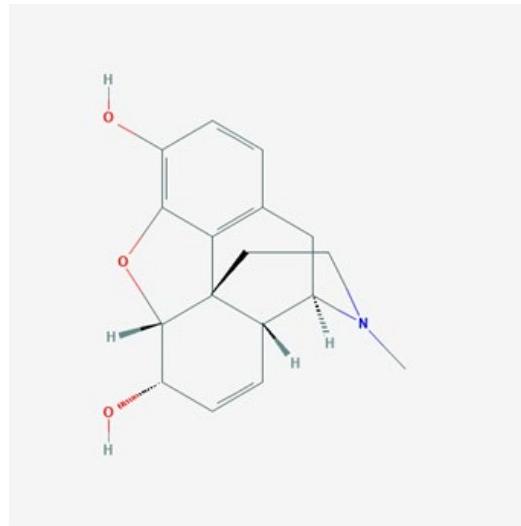
In the 1800s, new drugs built off morphinan were developed, including the naturally occurring opioids morphine, and its semi-synthetic derivative, heroin. These drugs, modified from the opium poppy, were more potent and more dangerous derivatives of the Molecule. Indeed, when morphine was first extracted from opium in the early 1800s, it was one of the most potent painkilling drugs (10 times more potent than opium). Heroin (first synthesized in 1897) was no different, but it was twice as potent as morphine. These drugs were certainly more potent, but the core Molecule was still present and still caused the same disastrous consequences of addiction, respiratory depression, and death when synthesized into drugs for

human consumption.³¹ As depicted below, heroin and morphine have, at their core, the Molecule, and closely resemble each other:

Heroin



Morphine



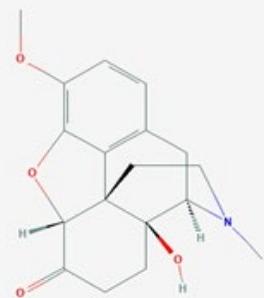
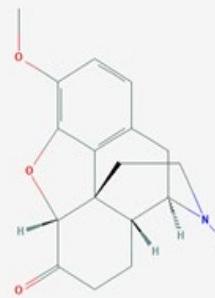
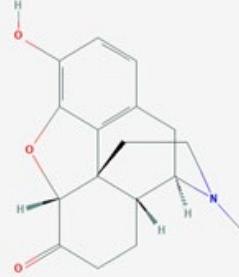
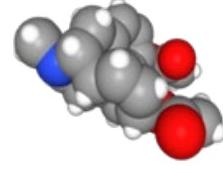
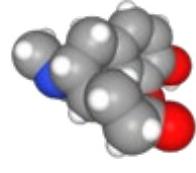
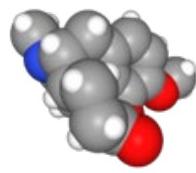
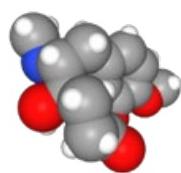
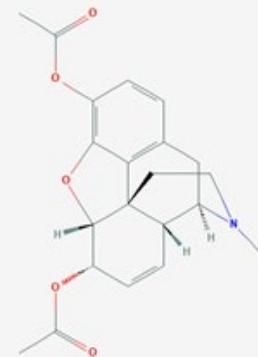
Unsurprisingly, these new drugs produced the same disastrous results seen with opium.

Indeed, morphine was rampantly abused in the late 1800s and early 1900s and created a generation of people addicted to the Molecule. Likewise, heroin produced an epidemic of drug abuse, addiction, and death in the early 1900s, was made illegal in 1924 and caused a crisis of addiction in the 1970s.

Despite all the havoc wreaked for thousands of years, and acutely in the United States in the 1800s and 1900s, drug makers continued the relentless pursuit of designing and selling synthetic opioid narcotics to treat pain, overlooking the history of the Molecule in pursuit of the

profits such a blockbuster drug could bring. Indeed, in the early 1900s, drug makers engineered a new set of semi-synthetic opioid painkillers, including oxycodone, hydrocodone, and hydromorphone.³³⁻³⁵ At their core, each of these opioids contained the Molecule and are functionally equivalent to known dangerous and illegal drugs, including heroin, and drugs like morphine that have caused rampant addiction in the United States. Ignoring all of this, Defendants sold hundreds of billions of MMEs oxycodone and hydrocodone into the United States between the mid-1990s and today.³⁶

Defendants' Drugs were no different than heroin or morphine in terms of their function, effect, and risk. This simple visual shows the nearly identical structure between the Defendants' Drugs and illegal drugs containing the Molecule such as heroin:

OxycodoneHydrocodoneHydromorphoneHeroin

As the next Sections describe, Defendants' Drugs were simply the most recent attempt to utilize the Molecule, despite its long history of wreaking havoc. As a result, the large-scale sale of Defendants' Drugs represents one of the worst preventable tragedies in United States history.

B. How Do Drugs Utilizing the Molecule Work?

Opioids utilizing the Molecule have attempted to mimic the internal way the brain and the body use natural opioids such as endorphins, and dynorphin (that blocks euphoria), to bind to the Mu receptor to produce pain relief. While this sounds like the body's natural way of using endogenous opioids to produce pain relief, numerous material differences explain how the use of opioids has caused such devastating consequences.

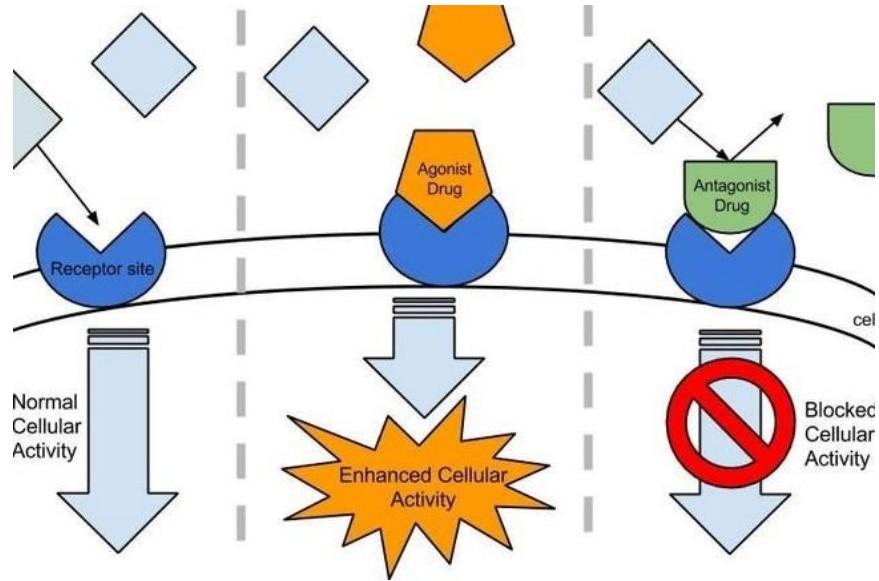
Defendants' Drugs, as well as heroin and illicitly manufactured fentanyl, are called a "full agonist" and are functional equivalents.¹ Additional categories of opioids, partial agonists and antagonists, are also relevant to the opioid epidemic for other reasons,ⁱⁱⁱ including their use in treatment and harm reduction; however, they will not be the focus here as the Defendants' Drugs were primarily full agonists.

The term full agonist refers to the ability of a molecule to bind a receptor and fully activate it. In the case of heroin and the Defendants' Drugs, they bind the mu-opioid receptor

ⁱⁱⁱ Partial Agonists: Opioid partial agonists are not as potent as full agonist opioids. However, they have enough intrinsic activity at the mu-opioid receptor to relieve withdrawal and pain, but not enough to significant intoxication, overdose, or death. Therefore, this class of opioids (specifically, buprenorphine) is often used in addiction treatment.

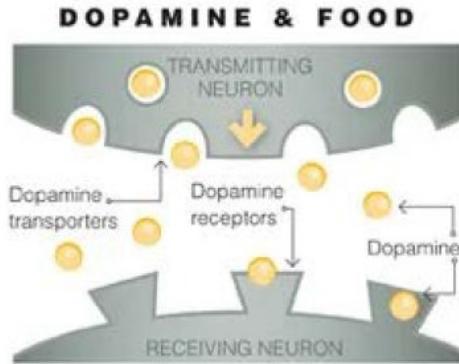
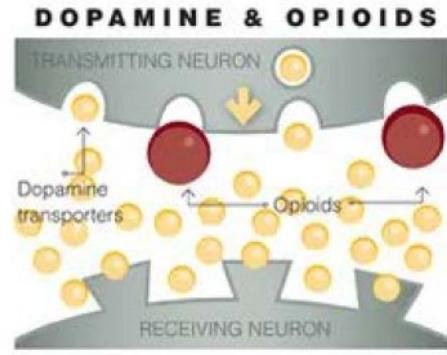
Opioid antagonists: A category of opioids that have a high affinity for mu-opioid receptors, but no intrinsic opioid receptor activity and, therefore, produce no opioid effect. These molecules can be useful in reversing overdose (naloxone), or in helping reduce relapse and maintain abstinence when someone has stopped using opioids (naltrexone).

and fully activate it producing enhanced cellular activity that, if unchecked, can lead to respiratory suppression and death. This basic mechanism is illustrated as follows:



This enhanced cellular activity may block the body's pain signals, making the patient feel relief in the short term. Very problematically, however, opioids cause a host of other reactions that can be both dangerous and deadly, including hijacking the body's natural reward system to produce an uncontrollable flood of dopamine that often creates an inflated sense of pleasure. This, in turn, can trigger the disastrous consequences of addiction, misuse, overdose and death in a person taking the drug.¹⁰

The National Institute on Drug Abuse illustrates this basic concept as follows:

Normal Dopamine Response:^{iv}Dopamine & Opioids:

When opioids hijack the body's reward system by producing a flood of dopamine in this way, the body has a strong desire to replicate that feeling that often triggers the progression to additional opioid use, misuse and addiction, as further discussed in Section D, below.⁴⁰⁻⁴⁵

C. Opioids' Interference with the Body's Natural Pain System

External opioid drugs attempt to mimic the body's natural response to pain. While this sounds good and can be critical for short term severe pain relief in acute situations, the attempt to mimic the body's natural process falls far short in chronic pain situations and has significant negative consequences independent of the severe risks of addiction, overdose, and death discussed in Section 5 of this Report.

In short-term, acute pain situations, such as during surgery or immediately post-surgery, prescription opioids can be an important mechanism of pain relief because they allow us to increase the mobility of the patient, decrease the patient's anxiety about the procedure or injury, and allow for a future perspective that significant pain does not allow.

^{iv} Graphic by Anna Perlich, National Institute on Drug Abuse, <https://www.drugabuse.gov/>.

When exogenous opioids are used to treat chronic pain, however, the many pathways in our brain and spinal cord rapidly recalibrate in negative ways.

1. Decreased production and dysregulation of natural endorphins:

When an opioid is introduced into the body to treat pain, the body's feedback loop senses that it does not need to make as much of its endogenous opioids because it receives a false signal that it already has enough opioid to address the pain. Not only are the body's endorphins not released, but over time the periaqueductal gray, the ventral medulla, and the dorsal horn begin to produce fewer endorphins. Endorphins are not only used for pain control but are integral components of mood stabilization, anger management, and fear abatement. With fewer endorphins produced, the ability to buffer pain and mood becomes nearly impossible. By artificially manipulating them, the reaction to any stimulus can produce disproportionate pain, anxiety, and fear.^{46,47}

2. Hyperalgesia:

As discussed earlier, the body's natural system of addressing pain attempts to address the nuance of each pain situation. The body's job is to make sure the brain gets the appropriate pain signal to address the type of pain a person is experiencing. When a person takes opioids like Defendants' Drugs, however, the drug masks the pain signal, so the person feels less pain. While this sounds appropriate, these drugs result in the brain receiving inaccurate information and ramping up the pain signal sent to the brain. Essentially, the body tries to overcome the opioid drugs to ensure the pain signal breaks through and gets to the brain. The signal to the brain then begins to exaggerate the pain the patient is perceiving. When this occurs, pain signals become more frequent, and any little thing will trigger them, as opposed to requiring a significant pain

source to generate this kind of response. This phenomenon is called hyperalgesia. Hyperalgesia is a physiological phenomenon that occurs when pain is produced from nonpainful stimuli. Mild touch can even provoke pain in this situation. The condition occurs because the patient's endorphins are not dampening the pain signal because of the response to the outside opioids.²⁶⁻

28,48,49

When opioids are introduced, all four of the ascending tracts are sending out as much signal as they can, and the patient does not have the norepinephrine inhibitory signal that he or she would normally have from the periaqueductal gray to the locus coeruleus (see Schedule 1). This mechanism is not able to work properly because the periaqueductal gray is clouded with the outside opioid and is not able to turn on that signal adequately. No matter what the patient does, the pain stays the same and, in many cases, gets worse because the patient is not able to produce the needed endogenous opioid peptides in the periaqueductal gray or dorsal horn. For a lot of these patients, it feels like they are on fire because the c-fibers (small unmyelinated pain fibers) also start to ramp up their signal causing widened and worsening terrible pain.

3. Behavioral Issues

All this physiology and neurobiology, however, cannot be seen from the outside. Instead, one sees the outward manifestations of the underlying neuroscience, including:

Behavioral Changes (Pain Behaviors): These behaviors include rapid escalation or changes in mood, emotions changing quickly without awareness or control, anger, crying, anxiety, low emotional distress tolerance, irrational thinking or behaviors, and excuses for behavior.

Medication "Issues": Perceiving more pain often leads to early refills, seeing several doctors, going to the ER for medications, taking more than prescribed dose, abnormal

attachment to medications, or buying medications “on the street;” all problems that have contributed to the opioid epidemic we are experiencing today.

D. Serious Risks Associated with Defendants’ Drugs

Not only do Defendants’ Drugs have drastically negative consequences for the body’s natural system of regulating pain and the host of negative issues related to the disturbance of the body’s natural pain regulation system, but they carry with them serious, severe and predictable risks of addiction, dependence, tolerance, withdrawal, respiratory depression, overdose, and death.^{1,50-55} These known risks, coupled with the lack of efficacy for long term use (addressed in Section E, below), meant that Defendants’ Drugs had no place being widely distributed and sold in the United States from the 1990s to today. Indeed, once a population was widely exposed to Defendants’ Drugs, one needs look no further than basic neuroscience to understand why we are experiencing an opioid epidemic in the United States, and acutely in West Virginia, including in the Cabell-Huntington Community.

1. Addiction

The American Society of Addiction Medicine (ASAM) states that “[a]ddiction is a treatable, chronic medical disease involving complex interactions among brain circuits, genetics, the environment, and an individual’s life experiences. People with addiction use substances or engage in behaviors that become compulsive and often continue despite harmful consequences.” This is reflected in an individual pathologically pursuing reward and relief by substance use and other behaviors. Addiction is characterized by an inability to consistently abstain, impairment in behavioral control, craving, diminished recognition of significant problems with one’s behaviors and interpersonal relationships, and a dysfunctional emotional

response. Like other chronic diseases, addiction often involves cycles of relapse and remission. Without treatment or engagement in recovery activities, addiction is progressive and can result in disability or premature death.^{56,57} Addiction to opioids is also referred to as Opioid Use Disorder (OUD). Notice should be taken that the defining aspects of the definition of addiction rely on behavior and not the current presence or absence of a drug.^{2,45,58-61}

The American Psychiatric Association (APA) has put forth a series of clinical criteria for use in diagnosing Opioid Use Disorder as follows:⁶²

Opioid Use Disorder: OUD is defined as two or more of the following within a 12-month period:

1. Using larger amounts of opioids or over a longer period than was intended
2. Persistent desire to cut down or unsuccessful efforts to control use
3. Great deal of time spent obtaining, using, or recovering from use
4. Craving, or a strong desire or urge to use a substance
5. Failure to fulfill major role obligations at work, school, or home due to recurrent opioid use
6. Continued use despite recurrent or persistent social or interpersonal problems caused or exacerbated by opioid use
7. Giving up or reducing social, occupational, or recreational activities due to opioid use
8. Recurrent opioid use in physically hazardous situations
9. Continued opioid use despite physical or psychological problems caused or exacerbated by its use
10. Tolerance (marked increase in amount; marked decrease in effect)

11. Withdrawal syndrome as manifested by cessation of opioids or use of opioids (or a closely related substance) to relieve or avoid withdrawal symptoms.

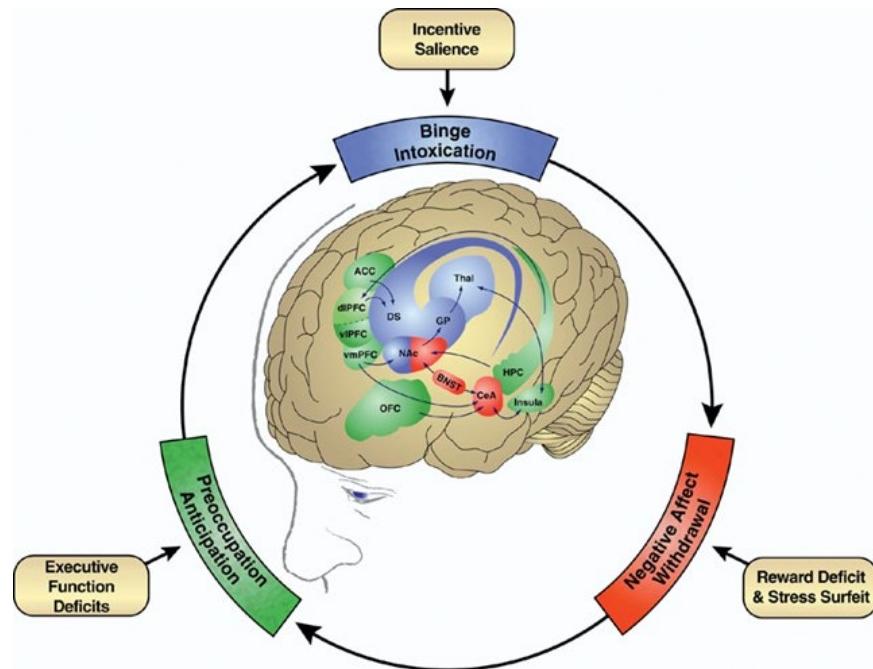
The severity of OUD is categorized as mild (presence of 2-3 symptoms), moderate (4-5 symptoms), or severe (6 or more symptoms). These symptoms of OUD and the resultant impacts on health and safety have been at the core of the opioid crisis we are experiencing across the United States, and acutely in West Virginia, including the Cabell-Huntington Community.⁶²

One of the primary reasons that exposure to opioids, including Defendants' Drugs, leads to addiction and the resultant behavioral impacts of addiction is that the drugs cause fundamental changes to the brain, including a profound impact on the neuronal circuits that are involved in processing responses to rewarding stimuli and motivating behavioral actions, negative emotions, decision-making, and cognitive control turning drug use into compulsive behavior. The fact that these changes are progressive and, once developed, are long lasting, persisting even after years of drug use discontinuation, is what makes addiction a long-term, chronic, and relapsing disease.^{63,64} As the CDC states, “[A]nyone who takes prescription opioids can become addicted to them.” No patient is immune to addiction.^{64,65}

Associated abnormal behaviors, such as those that are associated with OUD, are the result of dysfunctions in brain circuitry that are necessary for everyday activities. Indeed, the structural changes that opioids produce on the brain modify and diminish how the brain perceives the value of natural rewards. Those changes also diminish the capacity of the brain's prefrontal cortex to exert normal cognitive control over drug-seeking behavior, while enhancing the brain's response to drug-related cues and stimuli. At a behavioral level, the individual transitions from experiencing the acute effects of the drug, to patterns of recreational use, and

then to pathological states of abuse and addiction. The persistence of addiction is based on the remodeling of synapses and brain circuits, like the process of long-term associative memory, in which drug-associated environmental stimuli or cues have inordinate power to direct behavior. The persistence of changes in brain activity of persons who are addicted to an opioid helps to explain the persistence of their drug-related behaviors, their altered motivational hierarchies, and their responses to cues and cravings, all of which may persist for long periods after substance use has stopped.^{17,66-72}

As noted by Volkow and Koob, there are three general phases of addiction, each representing basic neurocircuitry linked to a functional domain and associated brain functional networks:



Binge/Intoxication phase:

The binge-intoxication stage via the neurocircuitry of the basal ganglia reflects the rewarding effects of drugs and the ways in which drugs impart motivational significance to cues

and contexts in the environment. This is termed incentive salience, which is experienced as “well-being,” “high,” “euphoria,” or “relief,” depending on the degree of tolerance to the rewarding effects of the drug.

As described briefly above, during the binge-intoxication stage, opioids, including Defendants’ Drugs, cause large surges of dopamine and the release of opioid peptides. Dopamine is one of most influential chemicals in the brain. Humans need dopamine because it is the chemical responsible for motivation. Dopamine is responsible for us making a friend, creating a mother-baby bond, and motivating us, when we do good, to do better. So, when someone pats you on the back and says, “good job,” you go and do something more significant. This happens because your dopamine has been increased, which drives you towards more reward.

Given dopamine’s fundamental importance, scientists have researched how much dopamine we need to survive. On a normal day, the brain produces dopamine in a relative range of about 50 ng/dL (ranges are from the shell of the NAc). That level of dopamine motivates a person to go about the normal activities of daily life, such as getting out of bed, getting a cup of coffee, and going to work. From a person’s worst day to their best day, the amount of dopamine released in the brain typically ranges from 40ng/DL to 100 ng/dL.^{44,73-85}

When an opioid is added into the brain, however, the drug causes the brain to produce more than 10 times the amount of dopamine our brain (Nucleus Accumbens and Ventral Tegmental Area) normally produces, over 900 ng/DL. Such an immediate surge in dopamine creates a “high” that people who experience it describe as euphoric. In the brain, the desire to repeat that euphoria, caused by the opioid-produced spike in dopamine, causes the person who experienced that euphoria to want to repeat that feeling. This produces repeated use, over time,

in increasing amounts to try to achieve the same euphoric feeling. With continued and increasing use, chasing the euphoric feeling becomes all-consuming, replacing normal activities that produce happiness. Over time, the things that normally produce happiness start to pale in comparison to the drug. The brain perceives it needs the drug for survival, not overt pleasure.

Over time, opioid use, such as taking Defendants' Drugs, causes a reduction in the dopamine levels the body produces naturally. At this point, people taking opioids must take the drug just to return them to the normal level of dopamine released in the brain. If the drug is removed, a regular opioid user's dopamine plummets to non-therapeutic levels (the level that makes it hard to get out of bed, go to a job interview, or even take care of oneself or one's family). When we lack dopamine, the body craves it, and when an individual craves dopamine, he or she transitions into survival mode leading to primal action. That primal action is exhibited in behavior the person would normally never exhibit, such as stealing from a relative or leaving a child. Their brain is telling the opioid user that he or she is not going to survive if he or she does not get dopamine, and the thing he or she believes gives him or her the dopamine is opioids. All these changes in the brain make a person taking opioids captive to the opioid and makes continuing to take it a perceived matter of survival. This explains why, if prescription opioids are cut off, people taking prescription opioids will seek illegal, more-available drugs such as heroin or fentanyl (something they could never have imagined doing) because the alternative of not having the drug is not seen as an option.

These risks increase when there is increased exposure to opioids through higher doses or longer durations of use.^{86,87} Additionally, there is compelling research showing iatrogenic addiction is a significant risk of exposure to prescription opioids such as Defendants' Drugs.⁸⁸

Finally, as we have seen in the current opioid epidemic, the inability to achieve the dopamine levels a regular opioid user craves, and often inevitably, leads that person down a predictable path of increasing use, increasing the potency of the drugs they are taking, and eventually switching to different types of opioids such as illicit heroin or fentanyl, or different types of drugs such as methamphetamine, just to return to their previous euphoric state, or even just to feel normal. Indeed, these are predictable paths, once a person is exposed to opioids and is an entirely foreseeable consequence of exposing individuals to opioids, especially in unprecedeted amounts and dosages.

Negative Affect/Withdrawal:

Addiction to drugs has been conceptualized as a reward deficit disorder. That is true when a person is in the early stages of addiction. However, once a person transitions to compulsive drug use, negative reinforcement mechanisms (the desire to avoid withdrawal) play a substantial role in continued, escalated drug use. Negative reinforcement is a behavioral mechanism whereby more significant drug-taking is strengthened by the alleviation of the negative emotional state precipitated by the absence of the drug. As with the reward functions of the brain, structural changes in the brain caused by opioids, including Defendants' Drugs, create neuroadaptations in the brain reward, executive, and stress systems that are key drivers of the compulsion to continue drug intake despite adverse consequences.^{1,10,41,89}

The power of avoiding withdrawal in perpetuating opioid addiction cannot be understated. When the opioid is removed from the system, the locus coeruleus reflexively releases a large amount of norepinephrine (adrenaline), creating an exaggerated fight or flight response. Patients often equate withdrawal as their number one fear and will do "anything" not

to experience it. This includes stealing from family, selling one's own body, and committing significant crimes just to get the dopamine surge that will stave off the agony. Even when ready to get help for addiction, the fear of withdrawal creates a reflex to run in patients, because most of the "terrible" things that they have done were as a result of the fear response associated with withdrawal. Indeed, withdrawal can include severe symptoms such as:⁹⁰⁻⁹⁵

- craving of the drug,
- lacrimation,
- severe muscle aches/cramps,
- abdominal cramps,
- nausea or vomiting,
- diarrhea,
- pupillary dilatation,
- piloerection,
- recurrent chills,
- tachycardia,
- hypertension,
- restless sleep.

It is often the overpowering desire to avoid these symptoms that drives patients to seek more and more opioids and may drive people to seek the drug via prescription or illicit means. In other words, avoiding the extreme lows and terrible physical symptoms of withdrawal often drive people to take more and more opioids or to be unable to stop taking opioids. By exposing a population to these addictive and dangerous drugs, it was a predictable and foreseeable

consequence of that massive exposure that diversion and illegal markets would follow. Indeed, once someone is hooked on opioids, it is an utterly unrealistic expectation to expect them to simply stop taking the drugs, to be able to prevent taking them in increasing amounts or to be able to prevent themselves to transitioning to illegal use if supply becomes restricted or when the drug ceases to stave off the withdrawal consequences or achieve the same euphoria as it once produced.

Preoccupation/Anticipation:

The preoccupation-anticipation (“craving”) stage reflects the impulsivity and loss of control over drug-taking, termed loss of executive control. Over time this becomes a reflexive response when the signals from the lateral habenula to the orbitofrontal cortex become solidified. Indeed, a hallmark of addiction involves poor inhibitory control and poor executive function, which are mediated by prefrontal cortical regions in the brain. That is because regions of the prefrontal cortex (PFC) are selectively damaged by chronic intermittent drug use and result in poor decision-making that can perpetuate the addiction cycle. Adaptations also appear to occur in regions that are innervated by mesolimbic DA circuits (including the NAc, amygdala, hippocampus, and PFC)(*see Schedule 1*), which may contribute to greater salience of the drug and drug stimuli and the lower sensitivity to natural reinforcers.

The craving stage generated by opioids is extremely powerful and explains why those who are exposed to these drugs are often unable to stop using them. Relative to other cravings, such as when a person is starving or dehydrating, the power of opioid cravings has been measured to be exponentially more powerful.

All these three phases help explain why exposure to opioids is so highly risky. Indeed, once exposed, human beings suffer nearly immediate neurological changes that can lead to cycles of addiction so powerful that they are nearly impossible to break. All three of these phases explain why these drugs trap the individuals who take them and have produced the opioid epidemic we see today.^{40,96-100}

2. Overdose and Death

Opioids carry with them a serious risk of overdose and death. Opioids affect the central part of the brain that regulates breathing, slowing breathing down. A significant risk to taking opioids is that breathing slows to the point of fatal respiratory depression. This serious risk increases as opioid doses increase. When a person stops breathing, the oxygen supply to their brain and heart plummets and the victim can die from cardiac arrest secondary to respiratory arrest.

Opioid overdose has unfortunately become all too common in the United States and in the Cabell Huntington Community (see Sections 8, 10, below). Driven by opioids, drug overdose is now the leading cause of unintentional injury death in the United States.¹⁰¹ According to CDC data, 245,218 people died from an overdose from prescription opioids between 1999 and 2018; 115,568 died from a heroin overdose; and 124,486 died from non-methadone synthetics, primarily fentanyl.¹⁰² For every death, however, there are many more overdoses that do not result in death.¹⁰³

Individuals with OUD are at a high risk of death.¹⁰⁴⁻¹⁰⁶ Specifically, in West Virginia, a study of unintentional prescription overdose deaths found that four out of five decedents (80%) had a history of a substance use disorder.¹⁰⁵

3. Tolerance, Misuse, and Dependence

The term “addiction” is often used by practitioners outside the field of addiction medicine, as well as by laypeople, to describe a spectrum of behaviors ranging from dependence and misuse to a diagnosed use disorder. In addiction medicine, these terms have specific meanings. The American Society of Addiction Medicine (ASAM) and the American Academy of Addiction Psychiatry (AAAP) recognizes the following definitions (misuse comes primarily from SAMHSA):

- Tolerance: A state of adaptation in which exposure to a drug induces changes that result in a diminution of one or more of the drug’s effects over time.¹⁰⁷
 - Opioid tolerance develops very quickly and in a more rapid fashion than other chemicals such as alcohol. There is also differential development of acute tolerance to analgesia vs. respiratory depression with opioids, making them particularly dangerous in some ways, including the development of dependence and addiction.
- Misuse: Use of a drug in any way that a doctor did not direct a person to use it, including (1) use without a valid patient-specific prescription; (2) use in greater amounts, more often, or longer than the patient was told to take them; or (3) use in any other way a doctor did not direct the patient to use them.¹⁰⁸
- Physical dependence: A state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction, decreasing blood level of the drug, and/or administration of an antagonist.^{56,107}

Even though addiction, misuse, dependence, and tolerance are defined terms in addiction medicine, the difference between them is often not easily designated, and the distinctions between them in the context of opioid use is sometimes unclear.^{1,109} There are serious risks and negative consequences associated with all parts of this spectrum. Indeed, patients who are given prescription opioids can develop dependence very quickly and are at significant risk of the progression to misuse or use disorder, including the use of illicit opioids such as illicitly manufactured fentanyl and heroin. What is certain is that all have real and very serious consequences for millions of people in the United States today and must be considered in addressing the opioid epidemic in the United States, in West Virginia, and in the Cabell-Huntington Community.

Tolerance:

When drugs such as prescription opioids are used repeatedly over time, tolerance often develops. Tolerance occurs when the person's body no longer responds to the drug in the way that it initially responded, i.e., it requires a higher dose of the drug to achieve the same level of response achieved initially.⁵⁷ Taking more of the drug over time can lead to dependence and potentially addiction. The development of tolerance alone is not addiction, although many drugs, like Defendants' Drugs, that produce tolerance also have addictive potential. It has been proven that in part because of tolerance, dose escalation with opioids leads to dependence and is correlated with progression to addiction.^{87,110}

One of the most serious issues with opioid tolerance is how quickly it develops (as previously mentioned) but more concerning is how rapidly it can recede. Often, when patients are unable to maintain their previous dose (for whatever reason), they can overdose upon

returning to that dose even a few days or weeks later. This is all too common, especially in those with OUD who attempt detoxification either voluntarily (treatment without appropriate medication) or involuntarily (such as incarceration).

Misuse:^v

SAMHSA defines misuse of medications as including: (1) use without the patient's own prescription; (2) use in greater amounts, more often, or longer than the patient was told to take them; or (3) use in any other way a doctor did not direct the patient to use them.¹⁰⁸ The WHO Lexicon defines misuse as use for a purpose not consistent with legal or medical guidelines.¹¹¹ It notes that the term "misuse" may be less pejorative than the term "abuse." In its screening efforts, the US Department of Veterans Affairs describes misuse as the target of screening and intervention.¹¹² The definition in that context has been the spectrum of use that increases consequences. But "misuse" is not an accurate descriptor for "dependence" or "addiction" because it minimizes the seriousness of the disorder and suggests the disorder is due to a choice (to "misuse") the substance. It is important to note that patients with any form of misuse often need some form/level of intervention to prevent progression to addiction; that can include psychological and medical interventions depending on their specific case.

Dependence:

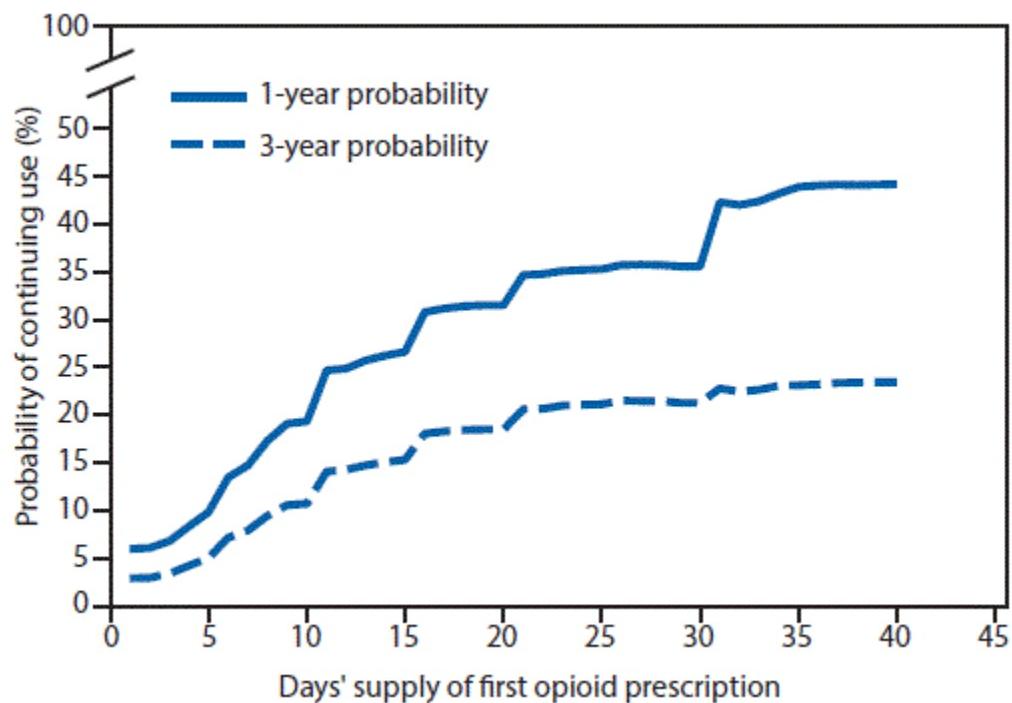
Dependence is defined by a state of adaptation that is manifested by a drug class-specific withdrawal syndrome that can be produced by abrupt cessation, rapid dose reduction,

^v Misuse is synonymous with "non-medical use."

decreasing blood level of the drug, and/or administration of an antagonist. In other words, a state in which an organism functions normally only in the presence of a drug. When assessing the risks of opioids, the substantial physiological consequences of dependence are often not discussed at length and the risk is significantly underrepresented. The risks are actually very significant and cannot be emphasized enough in the discussion of how opioids are uniquely addictive and how to prevent new cases of addiction as well as treat a population of people who are at risk of progressing to misuse and addiction. Dependence involving opioid narcotics carries very real and very severe consequences, not the least of which is the clear risk of transition to misuse and addiction.

As discussed above, one of the primary drivers of dependence, which puts dependent individuals at risk of misuse and addiction, is the powerful symptoms of withdrawal that occur when a person dependent on opioids ceases taking them. *See Section 5, above.* As with addiction, it is often the powerful desire to avoid these symptoms that drives patients who are dependent on opioids to seek more and more opioids. This may drive people to seek the drug via prescription or illicit means. In other words, avoiding the extreme lows and terrible physical symptoms of withdrawal often drives people to take more and more opioids or to be unable to stop taking opioids. From a clinical standpoint, opioid withdrawal is one of the most powerful factors driving opioid dependence, misuse, and addictive behaviors. Given the known high rate of transition from dependence to misuse/abuse, this clinical situation must also be addressed with appropriate evidence-based treatment modalities (as further addressed in Section L, below).

One of the exacerbating risks of taking prescription opioids, as opposed even to other addictive drugs, is how quickly patients develop dependence to these drugs and the likelihood of suffering withdrawal.^{10,25,109} Even short-term prescriptions for opioids are not without serious consequences in this regard. Physical dependence can occur in as little as one week. According to a recent CDC report, the transition from an initial opioid prescription to chronic use begins very early on. Even a one-day opioid prescription carried a 6 percent risk of use at one year later and a 2.9 percent risk of use at three years later.^{36,113} The sharpest increases in the likelihood of long-term use came at five days after the initial prescription, with another spike seen at one month. Patients given a longer-lasting prescription—a week or a month—at the outset were the most likely to fall into long-term use. Among people given enough pills for eight days or more, 13.5 percent were still using them a year later. Among those given a month-long prescription, that rate climbed to 30 percent.¹¹⁴



4. Difficulty Tapering

A critical factor in the opioid epidemic in this country today is the fact that so many people are dependent or addicted to prescription opioids, and that once that occurs, it is extremely difficult to get people to stop taking these powerful drugs. In fact, patients with dependence or addiction to opioids often require long-term maintenance on medications, primarily because of physiological dependence and the withdrawal that can occur if patients are suddenly removed from these drugs.

These basic facts, however, are not new knowledge. As early as the 1950s, leaders in the field of addiction treatment recognized that getting dependent or addicted patients off opioids was not as simple as eliminating the drugs. In the 1950s and 1960s, it was theorized that there would be a need to continue the opioids indefinitely once the brain had optimized itself for continued use.¹¹⁵

This basic principle has not changed since that time. Recent studies demonstrate that, although tapering can be achieved, significant challenges exist for those dependent on the medications. It has been demonstrated that many patients can be tapered, but not without significant risk of morbidity and mortality.¹¹⁶⁻¹¹⁸

All these serious risks arise as a result of exposing patients to opioids, even for a short duration. All of these risks increase when patients are exposed to opioids for longer durations and higher doses. It is not as simple as just stopping a medication. There is real risk that comes from just being on opioids for more than a few days.

E. What is the Appropriate Use of Opioids to Treat Pain?

The significant and severe risks discussed above would heavily weigh in favor of very limited use of drugs that can provide significant benefit only in certain limited contexts. One of the terribly tragic aspects of the current opioid crisis is that the benefits of opioids, including Defendants' Drugs, for treatment of anything other than acute pain relief, or for use in palliative care settings, has never been proven. Indeed, there are now a number of studies that show that with the exception of acute traumatic pain, medications like acetaminophen, ibuprofen, celecoxib, gabapentin and pregabalin are just as effective as opioids for post-acute trauma, postsurgical pain, and chronic non-malignant/non-cancer pain.^{1,114,119-123} The risk-benefit assessment of the use of opioids versus the use of other pain medications is, therefore, so lopsided towards risk, that any utilization of opioids outside of acute severe trauma or palliative care should be deeply questioned. Balancing opioids' severe risks with the lack of efficacy of opioids to treat chronic pain makes it obvious that opioids are of little to no use in chronic pain and should be used sparingly, if at all, to treat pain lasting more than 3-7 days.¹²⁴

Opioids pose only increased risk in the postoperative phase of treatment and there is no strong evidence for treatment of anything other than acute traumatic pain or severe acute trauma that they are any better than acetaminophen or nonsteroidal anti-inflammatory drugs for the treatment of acute pain. For patients with painful illnesses that limit the length of life, opioids can help to mitigate suffering. Judicious utilization of opioids in the setting of palliative care and hospice is still the core scope under which opioids may be used appropriately. We know that opioids are contraindicated in the treatment of diseases such as fibromyalgia and peripheral neuropathy. For elderly patients, those with sleep apnea or those that use other sedative

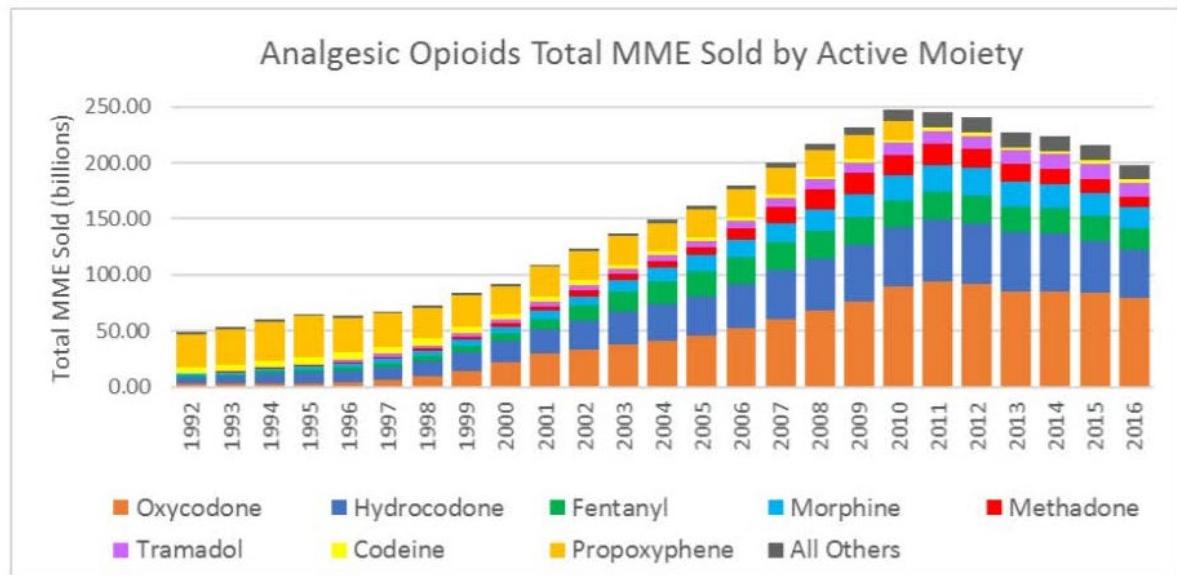
medications, opioids pose high risks, with little to no benefit. Recent literature even points to a contraindication for the utilization of opioids intra-operatively for elective surgeries given that they seem to worsen the postoperative course, make pain treatment more complex, and create a side effect profile that worsens operative outcomes. We have also identified that 21% to 29% of those started on long-term opioids for chronic pain (pain that lasts longer than the normal healing time or 3-6 months) risk the development of iatrogenic addiction and/or premature death secondary to accidental or purposeful overdose.^{50,125-127}

In conclusion, except for pain treatment in severe acute trauma, palliative care, and hospice treatment, opioids should be considered the approach of last resort when treating patients with acute or chronic pain. For all proper indications other than terminal cancer, palliative care, and hospice care, if prescribed at all, opioids should be prescribed with the lowest effective dose of immediate-release opioids taken only when needed.

F. Did the Use of Opioids in the United States Change over time? If Yes, in What Way?

Over the last 30 years, the utilization of opioids has changed significantly. Before the 1980s, opioid use to treat pain had been conservative. That was because historically, opioids had been shown to produce serious consequences, including addiction and the associated consequences of addiction. As discussed above, increases in the supply of opioids produced repeatedly devastating, and increasingly predictable consequences.

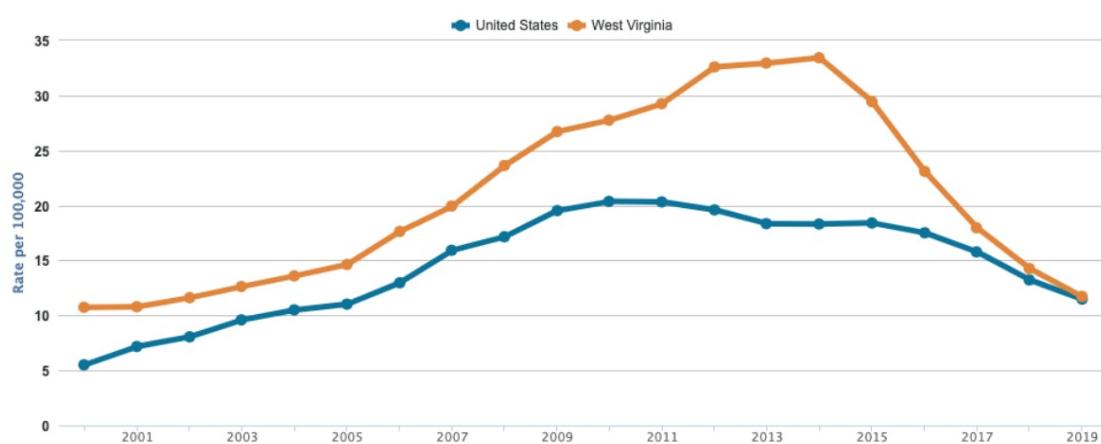
In the mid-1990s, however, a sea change in opioid utilization and supply began, hitting its peak between 2010. Billions of MMEs of opioids were sold each year, including by Defendants, topping out at approximately 250 Billion MMEs sold in the year 2010:¹²⁸

Figure 2: Total MMEs sold for aggregate opioid analgesic market – by active moiety

There was greater than a 600% increase in opioids dispensed in mg per person in the United States from 1997 to 2007.^{129,130}

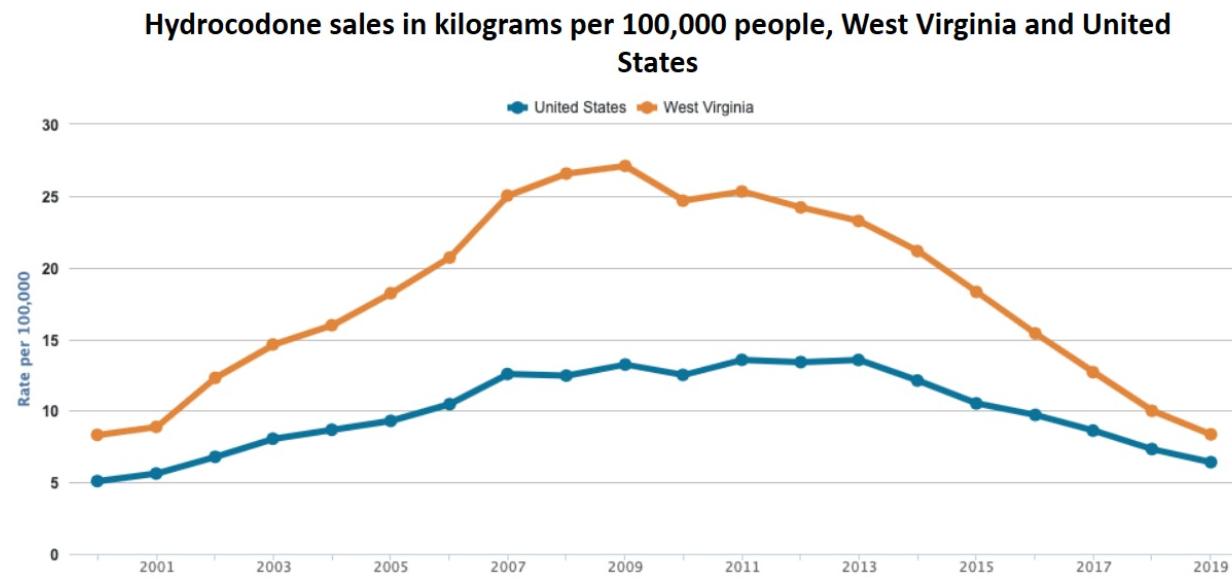
West Virginia was ground zero for this massive supply of prescription opioids. As illustrated by the following table, per capita Oxycodone supply into West Virginia dwarfed the numbers for the United States:¹³¹

Oxycodone sales in kilograms per 100,000 people, West Virginia and United States



SHADAC analysis of U.S. Drug Enforcement Agency's Automated Reports and Consolidated Ordering System (ARCOS) Retail Drug Summary Reports. State Health Compare, SHADAC, University of Minnesota, statehealthcompare.shadac.org, Accessed July 28, 2020.

Hydrocodone was even more dramatic:¹³¹



SHADAC analysis of U.S. Drug Enforcement Agency's Automated Reports and Consolidated Ordering System (ARCOS) Retail Drug Summary Reports. State Health Compare, SHADAC, University of Minnesota, statehealthcompare.shadac.org, Accessed July 28, 2020.

Between 2005 and 2014, Defendants sent billions of MMEs into the Cabell Huntington Community of 99,946 people. In fact, between 2006 and 2014, dispensers in the Cabell-Huntington Community received 127.9 million Dosage Units or 3.3 billion MME of opioids, enough opioids for every resident in Cabell County and the City of Huntington, WV to consume 142 Dosage Units or 3,650 MME every year from 2006 to 2014. (McCann Report at ¶ 17).⁷

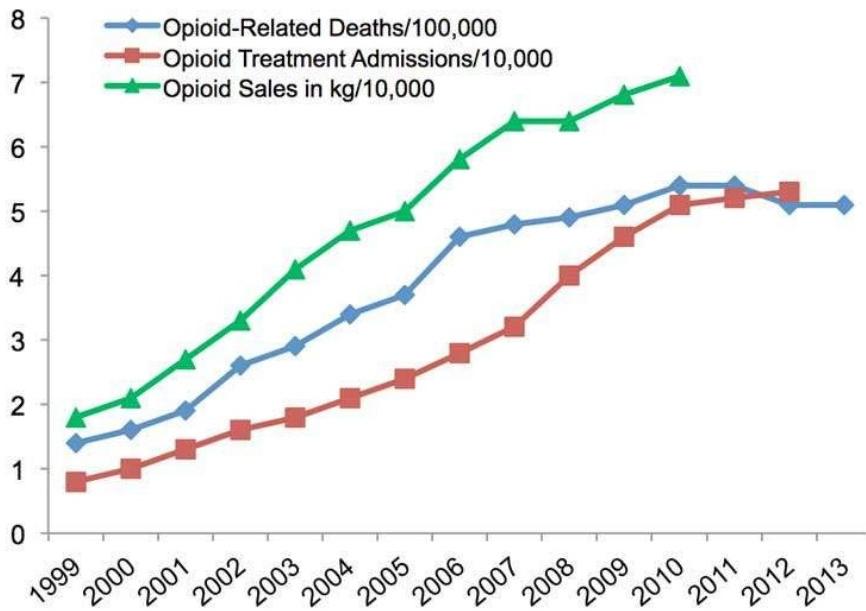
Despite the current opioid epidemic, the supply has remained dramatically elevated far above pre-1995 levels, while predictably, opioid users have increasingly turned to illicit drugs such as heroin, fentanyl, carfentanyl and methamphetamine.¹³²⁻¹³⁸

As detailed in Section E, there is not now, and never has been, a clinical basis for this dramatic shift. Even if the prevalence of pain has changed, opioids are not the solution, due to the lack of reliable evidence that they improve pain relief compared to non-opioid medications

that confer less risk. Moreover, Defendants Drugs contained the same active pharmaceutical ingredients and were functional equivalents of opioid drugs that had been shown to be highly addictive for centuries (see Sections B and D, above).

G. What were the consequences, if any, of any change in use and availability of opioids?

The tidal wave of pills created by the sale of Defendants' Drugs in record and rising numbers created an epidemic of addiction, misuse, overdose, and death. Indeed, simple graphs illustrate the rising devastation paralleling the rising sales of Defendants' Drugs:¹³⁹



The massive distribution of Defendants' Drugs has led us to the point where we have four major cohorts of patients who have been severely affected. The first cohort is those patients started on opioids for chronic pain, who developed physical dependence and/or hyperalgesia and who now have significantly impaired functional capacity because of this. The second cohort is made up of the over 11 million people who have developed high-risk misuse of opioids but do not yet meet the criteria for addiction. The third cohort is the over 2 million people in the United

States who developed OUD¹⁴⁰.^{vi} The most devastating effect of this inappropriate distribution of opioids is the fourth cohort of patients, which includes hundreds of thousands of people who died from opioid overdose over the past 20 years.¹⁰² Prior to COVID-19, opioid overdose was the leading cause of injury-related death and the outright leader in all-cause mortality for people under 50 years old.^{101,141} This surpassed car crashes and gun deaths with no sign of abatement. This effect was so large and widespread that it reduced the US life expectancy for the first time in modern history.¹⁴²

These affected populations produce a host of related societal impacts on the healthcare system, the child and family services system, public health systems and criminal justice systems that we have seen repeatedly in communities throughout the opioid epidemic, acutely in the Cabell-Huntington Community (see Section I-K, below)

H. What is the main cause of those consequences?

Dramatically increased exposure to prescription opioids is the critical factor that has caused the opioid crisis of addiction, abuse, morbidity, and mortality that we have seen over the past decade and continue to see today. Even though the development of the disease of addiction in individuals generally occurs as the result of three primary groups of factors: biology (genetics), environment, and exposure, biology and the environment do not factor into the equation unless patients are exposed to the chemicals and brain mechanisms are triggered.^{143,144} The entire neurobiological premise for addiction is that the brain structures must be “primed” with an abnormal rush of dopamine to begin the pathological behaviors that are an addiction. In

^{vi} These numbers are certainly undercounting as they do not take into account the homeless or prison populations and also do not take into account the millions of people who are dependent on prescription opioids.

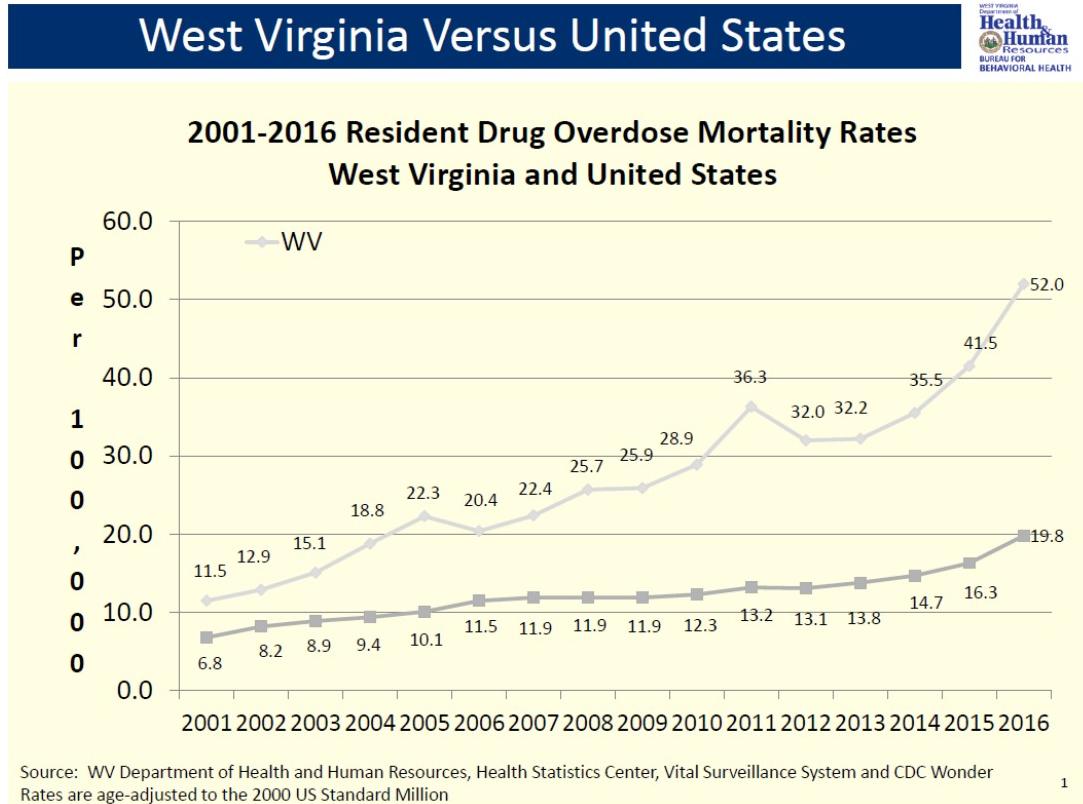
other words, if people, such as the public in the Cabell-Huntington Community are not exposed to opioids, the other factors cannot come into play. Exposure is the key factor in the addiction crisis, and the resultant societal impact, we see today.¹⁴³

The dramatic shift in the use and availability of prescription opioids from the late 1990s to present meant that people were exposed to vast and unprecedented quantities and doses of highly addictive narcotics with the foreseeable and severe risks that they carry in increasing and massive numbers. That exposure was a key component to the recent, massive increase of opioid addiction, dependence, misuse, and impact on mortality that we have seen in the United States;¹⁴⁵ a point that is starkly illustrated by the graphics in Section G above. From 1996 to 2011 there was a 1448% increase in the medical use of opioids. Over the same time period, opioid misuse increased 4680% and the number of people seeking treatment for OUD increased 187%.¹⁴⁶

Without the massive expansion of the supply of high potency opioids, including primarily by Defendants, we would not be dealing with the crisis that we have on our hands today.

I. Do we see those consequences prevalent in the Cabell-Huntington Community?

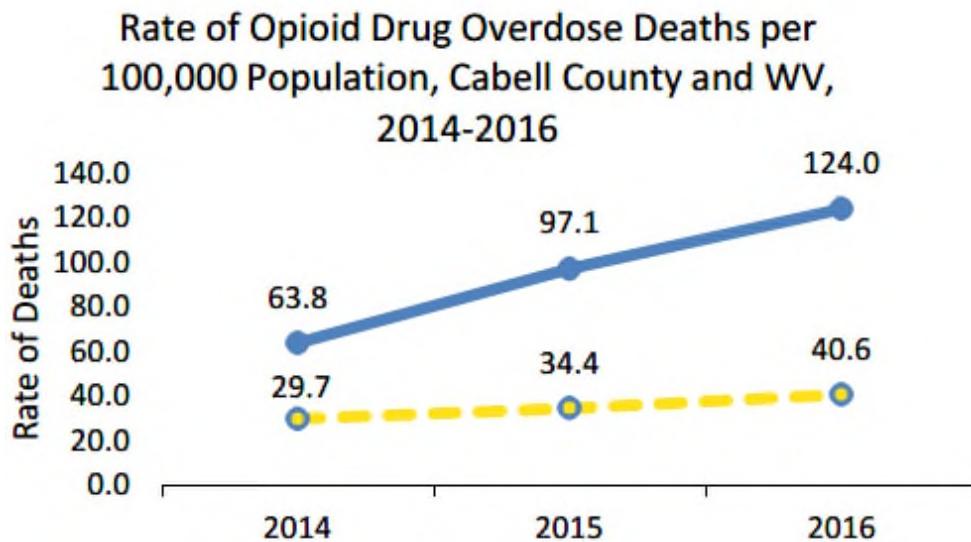
West Virginia was the state with the highest age adjusted death rate from opioids between 1999 and 2018.¹⁰⁵ The drug overdose death rate in West Virginia increased nearly every year since 1999, and far exceeds the United States average as shown here:



A June 4, 2020 report from the West Virginia Attorney General shows that the primary driver of these opioid related deaths has been the prescription opioids that Defendants were supplying. As noted in the report, “West Virginians feel the toll opioids have taken in every county, and it cannot be measured simply through loss of life. Opioid abuse and its attendant harms also reverberate across the healthcare system, the criminal justice system, and society as a whole.”^{147,148} Diverted drugs factored into roughly one-third of all fatal drug overdoses in 2016 that involved West Virginia residents. And rural and impoverished areas are particularly fertile grounds for diversion, as prescription-holders can earn a 1,200% profit from reselling a single pill.¹⁴⁹

The opioid epidemic in the Cabell-Huntington Community has been particularly severe.

Cabell County has the highest overdose rate in the state and its overdose rate is higher than the state overdose rate:¹⁵⁰



In 2018, Cabell County had the highest opioid overdose death rate of any county in the nation at 127.1 per 100,000.¹⁵¹

Further, just like the rest of West Virginia, the epidemic in the Cabell Huntington Community has not just been one of overdose and death. A broad coalition including local physicians, academic experts, government officials and law enforcement summarized the impact of Defendants' Drugs on the Cabell-Huntington Community as follows:¹⁵²

Cabell County, WV, has been ravaged by the harmful effects of the substance use epidemic. This has culminated in increased drug activity, the highest rate of overdoses and overdose deaths our nation has seen, and poor health outcomes. It has left in its wake individuals, families, organizations and an entire community that must now determine how to promote and achieve health and wellness across the lifespan.

Indeed, over the last decade:

Huntington readily recognized the severity of the issue seen in reported rates of overdose, overdose-associated deaths, and incidence of neonatal abstinence syndrome - the highest in the nation. The county has also been monitoring the sharp rise in the

incidence of infections and other diseases associated with substance use, including hepatitis B and C, sexually transmitted infections, endocarditis, and most importantly - a recent HIV cluster. In Huntington, as heroin became more popular and widespread, and the rates of infectious diseases, overdose, and overdose death quickly increased, this culminated in a shocking outbreak of 27 overdoses in just four hours in the city of Huntington on August 15, 2016.¹⁵²

Numerous local witnesses^{vii} describe the strain the supply of prescription opioids has put on the Cabell-Huntington Community and the resultant consequences of that exposure, including:

- Jan Rader, Fire Chief for the City of Huntington, described the opioid epidemic in Huntington as "horrific," and stated that "There's not one person in this area that I know that has not been touched or had collateral damage to them, themselves from the ... opioid epidemic. It is horrendous." Rader describes the effect of the opioid epidemic on the community stating "This is a war zone. This is a war zone for first responders. It's a war zone for children. That's all they know growing up, is death and destruction."
- Sue Ann Painter, the executive director of the board of registered nurses, testified that: "It's been financially devastating to people with substance use disorder and their families and their communities. It has emotional impact on all the individuals involved, and people die of overdose."
- Scott Lemley, former member of the City's Office of Drug Control Policy for the Huntington Police Department, testified that in 2015 "13.78 percent of the population of the County is addicted to something." "[I]t's horrible. It has affected every aspect of what we do in Huntington from social – It's socioeconomic. It affects the University; it affects our medical community; it affects our quality of life and our parks; it affects our first responders; it affects our property values."
- Hank Dial, City Manager for the City of Huntington and former Police Chief for the City of Huntington, testified that the drug problem in Huntington is so pervasive that every aspect of the police department had to deal with it: "[i]t was so encompassing, it affected every bureau."
- Ray Canafax, Deputy Chief of the Huntington Fire Department, testified that the epidemic "didn't know any bounds It was in all neighborhoods. It was in the best of neighborhoods and the worst of neighborhoods and the best -- the best of homes to the worst of homes."
- Rocky Johnson, former member of the Huntington Police Department Special Investigations Bureau, testified about doing everything within its ability to address

^{vii} A list of the deposition testimony I have been provided with and have reviewed in connection with rendering the opinions in this Report is contained in Schedule 4.

the opioid crisis, at their own peril, stating “police officers with our mental health, you know, and the fatigue, the compassion fatigue of seeing all this death and destruction and all of this.”

- Steve Williams, Mayor of the City of Huntington, testified “I know that people are dying here. I know that the level of overdoses that we’re having to deal with is causing a major disruption within our – within our community. I know it is a result of pills; I know it’s a result of heroin; I know it’s a result of other substances. We have babies that are being born exposed to substances; we have families that are being torn apart; we have parents who are dying. ... My city is suffering, and I believe your clients are also responsible for the suffering that has been placed upon my community.”

Likewise, numerous local task force reports have summarized the local devastation that we see as a result of Defendants exposing a wide swath of the population in the Cabell-Huntington Community to dangerous and highly addictive opioid narcotics.^{viii} I have reviewed the expert reports of Kathleen Keyes, Ph.D. and Professor Thomas McGuire. Rather than reproduce the facts and statistics cited therein about the devastating effects of Defendants' Drugs in the Cabell-Huntington Community, I incorporate them by reference herein as a further basis for the opinions expressed in this Section.

The devastation described in the Cabell-Huntington Community is, unfortunately, the all too common result of a dramatic oversupply of prescription opioids, including Defendants' Drugs. Indeed, in my work assisting communities around the country to devise solutions to the opioid epidemic in their communities, I have seen the pattern repeatedly and predictably.

J. Have opioids had a significant impact on public health?

In this past 12 years, I have been working to address the opioid epidemic in communities around the United States. In the course of this work, I have observed first-hand the impact of

^{viii} A list of the reports I have reviewed that form the basis for the opinions in the Section are contained in Schedule 4 to this Report.

opioids on public health. It has been severe. The impact of Defendants Drugs on public health in the Cabell-Huntington Community is particularly severe.

The CDC defines public health as the science of protecting and improving the health of people in their communities.¹⁵³ Overall, public health is concerned with protecting the health of entire populations. These populations can be as small as a local neighborhood, or as big as an entire country or region of the world. Based on this definition alone, it is clear that the ready access to opioids has created a significant public health crisis, particularly in the Cabell-Huntington Community (see Section J).¹⁵⁴⁻¹⁵⁸ Unfortunately, this crisis cannot be defined solely as an issue of mortality. While the average person with opioid use disorder who is not treated will have a final common pathway of incarceration, poverty or premature death, we will also see a significant impact on the families associated with these individuals and the communities within which they live. Because the system of addiction treatment was nowhere near able to take care of the avalanche of people coming into the system with an opioid use disorder, the public health system was overwhelmed from the beginning. Unique among the addictions, opioid use disorder created another public health issue with the increase in hepatitis C and HIV/AIDS amongst opioid injectors.

The public health impacts caused by the dramatic oversupply of opioids have been felt perhaps most acutely in West Virginia and in the Cabell-Huntington Community (see Section J). Indeed, I have been provided with the testimony of numerous community witnesses who describe the real and significant impact on public health and on the Cabell-Huntington Community caused by the surplus of Defendants' Drugs. See Schedule 4. Not only do community officials describe the serious public health crisis, but as described throughout this Report and in

the Expert Reports of Kathleen Keyes, Ph.D. and Professor Thomas McGuire, the Cabell-Huntington statistics are staggering and the facts and statistics cited therein provide additional basis for this opinion. I do not restate all the facts laid out by Professor Keyes or Dr. McGuire but incorporate them by reference herein.

K. Have opioids had a significant impact on public safety?

In the past 12 years, I have worked to address the opioid epidemic in communities around the United States. In the course of this work, I have observed first-hand the impact of opioids, including Defendants' Drugs, on public safety.

Ready access to opioids has significantly increased violence and criminogenic behavior and has completely overwhelmed law enforcement, the foster care system, the court system, and the prison system. As extensively discussed in this report, having an opioid use disorder means exhibiting behaviors that put individuals and others at significant risk. This includes behaviors such as driving cars while under the influence, getting into physical altercations, being a part of drug violence, having an increased risk of sexual assault, and putting a disproportionate burden on police, fire, and emergency medical services. With more than 75% of incarcerated persons meeting criteria for a substance use disorder and more than 35% of the incarcerated population meeting criteria specifically for an opioid use disorder, there should be little question about the risk to law and order and, ultimately, safety.¹⁵⁹⁻¹⁶⁵

The public safety impact caused by the dramatic oversupply of opioids has been severe in the Cabell-Huntington Community. I have been provided with the testimony of numerous community witnesses who describe the real and significant impact on public safety caused by the surplus of the Defendants' Drugs. See Schedule 4. As summarized by Dr. McGuire, the opioid

epidemic has led to burnout and trauma amongst police officers, firefighters, emergency medical technicians, and other first responders.^{152,166} The Cabell Huntington Community first responders face increased job stress due to ongoing dealings with large numbers of fatal opioid overdose fatalities. This increased stress on first responders results in government costs for education and wellness for firefighters, police officers, and EMS personnel. It also results in what has been called “compassion fatigue” that takes a personal toll, reduces job effectiveness, and results in difficulties retaining personnel. These human and economic tolls on first responders impact public safety. ^{167,168}

The expert reports of Kathleen Keyes, Ph.D. and Thomas McGuire, Ph.D., and the public safety facts and statistics cited therein provide an additional basis for this opinion. I do not restate all of the facts laid out by Professor Keyes or Dr. McGuire but incorporate them by reference herein.

L. What are the standards for treating opioid addiction and dependence?

Over the last decade, addiction medicine has developed a standard way to treat OUD and opioid dependence. Those standards are as set forth in the ASAM’s *National Practice Guideline For the Use of Medications in the Treatment of Addiction Involving Opioid Use*, the DSM-5, and *The ASAM Criteria*.¹⁰⁹

The standard treatment for OUD has three central components:

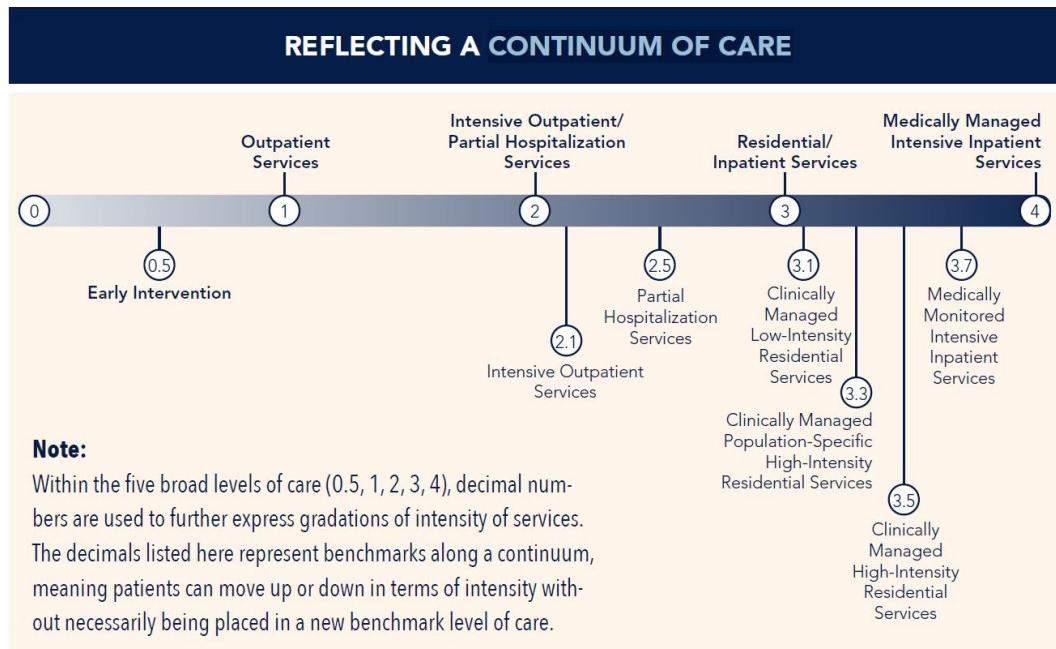
- Medical Treatment (which includes Medication Assisted Treatment, or “MAT” with drugs such as methadone, buprenorphine and naltrexone);
- Psychological Treatment; and
- Social Support (including case management and peer support).

This standard approach, often called the “biopsychosocial” approach, is endorsed by key organizations, including ASAM, SAMSHA, and NIDA, and is outlined in their respective publications.¹⁰⁹

As with all chronic relapsing diseases, every person will require different amounts of these treatments to build their unique multimodal treatment plan. Over the past 35 years, the American Society of Addiction Medicine has developed a set of criteria, called *The ASAM Criteria*, which is considered the gold standard for assessing the amount and the levels of care needed to treat a patient’s OUD. *The ASAM Criteria* is the most widely used and comprehensive set of guidelines for placement, continued stay, transfer, or discharge of patients with addiction and co-occurring conditions. Through *The ASAM Criteria*, adolescent and adult treatment plans are developed through a multidimensional patient assessment over five broad levels of treatment that are based on the degree of direct medical management provided, the structure, safety, and security provided and the intensity of treatment services provided.¹⁶⁹



The ASAM Criteria also sets forth a standard continuum of care that is used to determine the appropriate level of care across a continuum of individual circumstances (summarized below):



This continuum is the standard of care used in determining the appropriate level of placement for patients suffering from OUD.

As for those individuals who do not meet the criteria for the disease of addiction or are not physically dependent on opioids, the road is still treacherous. While we can slowly and deliberately wean patients off opioids, it must be individually driven. This is due to a number of factors, including increased risk of suicidal ideation when patients are forced off opioids, a transient increase in pain, mood instability, and an overall reluctance to be removed from a medication that patients were told by professionals was the best thing to treat the chronic pain. If not done properly, patients will experience withdrawal, which is easily perceived as worsening pain and increased anxiety. While the literature has been consistent in stating that weaning patients off opioids generally improves their pain or the cognitive disorders associated with the pain medication, we are hard-pressed to have patients agree with this during what can be a very bumpy process. Overall, this has been a much more difficult task than one may think. It has led

to unintended suffering and frustration amongst primary care providers and their patients, as well as a wholesale distrust of the healthcare apparatus.

M. CONCLUSION

There is a severe opioid epidemic in the Cabell Huntington Community that has been and will continue to be serious and long-lasting. This epidemic was caused by a dramatic exposure to prescription opioids, including primarily Defendants' Drugs. It was utterly predictable that exposing a population to these dangerous opioid narcotics in the quantities in which Defendants supplied them would lead to the kind of devastating public health and safety consequences we see in the Cabell-Huntington Community. While these disastrous consequences should have been easily foreseeable to Defendants, they are certainly not easily fixable. There are evidence-based solutions, with the appropriate resources, that can and should be implemented immediately that can begin to remedy the damage Defendants have caused.

Pursuant to 28 U.S.C. S 1746, I declare under penalty of perjury that the foregoing is true and correct.

Executed on August 2, 2020.

R. Corey Waller
R. Corey Waller, M.D., M.S.

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